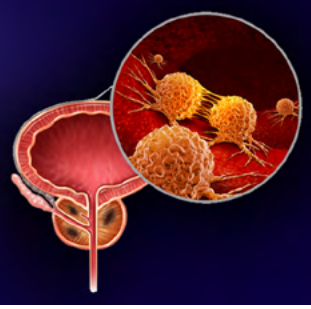
Prostate Cancer Practice Review™



Making Education Easy

Issue 21 - 2024

In this issue:

Abbreviations used in this issue:

ADT = androgen-deprivation therapy;
ASCO = American Society of Clinical Oncology;
CRPC = castration-resistant prostate cancer; **CT** = computed tomography;
FDA = US Food & Drug Administration; **MRI** = magnetic resonance imaging;
MSI-H = microsatellite instability-high;
NCCN = US National Comprehensive Cancer Network;
PET = positron emission tomography; **PSA** = prostate-specific antigen;
PSMA = prostate-specific membrane antigen.

Earn CPD

Royal Australasian College of Physicians (RACP) MyCPD participants can claim the time spent reading and evaluating research reviews as CPD in the online MyCPD program. Please contact MyCPD@racp.edu.au for any assistance.

Royal Australian & New Zealand College of Radiologists (RANZCR) members can claim reading related to their practice as a CPD activity under the category 'journal reading and web based no certificate *reflection required'. More info.

Welcome to the 21st issue of Prostate Cancer Practice Review.

This Review covers news and issues relevant to clinical practice in prostate cancer. It will bring you the latest updates, both locally and from around the globe, in relation to topics such as new and updated treatment guidelines, changes to medicines reimbursement and licensing, educational, professional body news and more. And finally, on the back cover you will find our COVID-19 resources, and a summary of upcoming local and international educational opportunities including workshops, webinars and conferences.

We hope you enjoy this Research Review publication and look forward to hearing your comments and feedback.

Kind Regards,

Dr Janette Tenne
Editor
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Clinical Practice

Prostate Cancer Foundation screening guidelines for prostate cancer in Black men in the U.S.

Although several American national guidelines – including from the American Cancer Society and The American Urological Association (AUA), in collaboration with the Society of Urologic Oncology (SUO) – advocate for early initiation of prostate-specific antigen (PSA)-based prostate cancer screening in high risk groups such as African American men or men with a first-degree relative with prostate cancer, to date a large proportion of this group have been precluded from screening prior to 55 years of age due to US Preventative Task Force recommendations that prevent insurance coverage. The latest iteration of the US Preventative Task Force Prostate Cancer Screening recommendations was published six years ago in 2018 and based on Grade C weak evidence demarcated the lower age for insurance subsidy of prostate cancer screening costs at 55 years of age, a differential of 10 years versus more modernised recommendations that suggest screening commence from 45 years in higher risk men. An update to these recommendations is in progress, but has not been released to date.

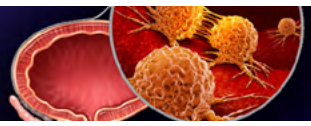
In order to disseminate clear recommendations for African American men and their clinicians regarding optimal screening practices, given the disparities between US national guidelines, the Prostate Cancer Foundation have provided novel evidence-based guidelines. The guidelines - consensus statements from an interdisciplinary expert panel including urologists, medical and radiation oncologists and patients advocates - were presented in a poster format at the 2024 American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium, held in January this year. Six guideline statements were provided based on review of 265 relevant studies published prior to April 2023. Level 3 & 4 evidence from observational cohort and modelling studies, respectively, indicates that prostate cancer develops up to nine years earlier (range, 3 to 9) in African American men than non-Black men and estimates that lowering the recommended baseline age for screening in this population by ten years – from 50-55 years to 40-45 years – would reduce prostate cancer-related deaths by 30% without compromising the rate of overdiagnosis.

The six consensus statements are as follows:

1. The benefits of screening in African American men generally overweigh the risks
2. Screening should be conducted by PSA testing with/without digital rectal exam
3. Shared decision-making between African American men and their clinicians is encouraged
4. Annual PSA-based screening may commence between the ages of 40 and 45 years
5. Decisions regarding whether to continue annual screening past 70 years of age need to be informed by life expectancy, health status, family history and prior PSA levels
6. Annual baseline screening may be initiated even younger (from 40 years of age) in African American men at higher risk due to family history and/or with known high-risk genetic variants

The full program from the 2024 ASCO Genitourinary Cancers Symposium can be found here

J Clin Oncol 2024; 42 (4_suppl. 264)



NCCN Clinical Practice Guidelines in Oncology® – Prostate cancer

Recent updates to the US National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for the management of prostate cancer have been published (version 4.2023). Designed for use by physicians, the guidelines provide a framework for the treatment of patients with prostate cancer that can be personalised across each step of the cancer journey based on disease characteristics, prognosis and patient preferences. Since their inception in 1996 the guidelines have undergone at least one annual update to reflect changes in regulatory regulations, the introduction of novel therapeutic or diagnostic agents and greater understanding of the responsiveness of various disease states to different therapeutic strategies. Advice covers multiple areas including:

- initial diagnosis
- initial risk stratification and staging workup for clinically localised, regional or metastatic disease
- primary therapy according to risk group
- monitoring
- PSA recurrence following radical prostatectomy and/or radiation therapy
- monitoring for PSA persistence/recurrence following maximal pelvic therapy
- Salvage systemic therapy for progressive disease according to castration-sensitivity status and the presence/absence of metastasis

The document also provides 12 principles sections: life expectance estimation, bone health, genetic and molecular/biomarker analysis, quality-of-life and shared decision-making, imaging, active surveillance and observation, androgen deprivation therapy (ADT), risk stratification, radiation therapy, surgery, local secondary therapy post-radiation and non-hormonal systemic therapy.

Four updates to the NCCN prostate cancer guidelines were published in 2023. Fundamental treatment recommendations include upfront combination therapy comprised of a doublet or triplet intensified ADT regimen such as ADT plus abiraterone, apalutamide, or enzalutamide; or ADT with docetaxel and abiraterone or darolutamide; or ADT with external beam radiation therapy to the primary tumour for all patients with metastatic castration-sensitive disease. The use of ADT monotherapy should be strictly reserved for cases of clear contraindications to intensification. Key revisions in 2023 iterations covered development in treatments for castration-resistance prostate cancer (CRPC), updates to radiopharmaceuticals such as radium-223 and lutetium (Lu)-177-prostate-specific membrane antigen (PSMA)-617, and expansion of acceptable imaging agents (fluorine [F]-18 piflufolastat PSMA and F-18 flotufolastat PSMA).

Salient revisions and updates in the first 2024 iteration include:

- the removal of direction to use anything other than active surveillance for patients stratified into the very-low-risk category with a life expectancy of 10 years or more. To be classified as very-low-risk all four of the following clinical/pathological features must be present: cT1c, Grade Group 1, PSA < 10 ng/mL, less than three prostate biopsy fragments/cores positive with ≤ 50% cancer in each and PSA density < 0.15 ng/mL/g
- the advice for adjuvant therapy following primary radical prostatectomy for patients with any low-, intermediate-, high or very-high-risk localised prostate cancer has been changed to suggest monitoring as the preferred strategy with consideration of early radiotherapy in cases of a detectable and rising PSA or PSA >0.1 ng/mL
- sections on PSA persistence/recurrence after radical prostatectomy or radiotherapy and systemic therapy for metastatic castration-sensitive disease heavily revised
- the addition of novel sections:
  - treatment and monitoring for progressive non-metastatic castration-sensitive prostate cancer after maximal pelvic therapy
  - Principles of bone health in prostate cancer
- Novel regimens suggested for metastatic castration-resistant adenocarcinoma including:
  - pembrolizumab for microsatellite instability-high (MSI-H)/mismatch repair deficient disease if no prior novel hormone therapy or chemotherapy and for progressive MSI-H disease after docetaxel
  - olaparib or rucaparib for progressive *BRCA* mutated disease after prior novel hormone therapy. Olaparib may also be utilised for HRR mutation other than *BRCA1/2*
- In terms of directions for imaging:
  - for initial bone imaging computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET)/CT or PET/MRI with F-18 piflufolastat PSMA, Ga-68 PSMA-11, F-18 flotufolastat PSMA, F-18 sodium fluoride, C-11 choline, or F-18 fluciclovine can be considered for equivocal results
  - Conventional imaging with CT or bone scan is not a required prerequisite to PSMA-PET in either initial staging or biochemical recurrence settings

The complete and most recent versions of these guidelines are available free of charge at www.NCCN.org (register to access). Guidelines for patients are also available online.

NCCN Clinical Practice Guidelines in Oncology® - Prostate cancer early detection

In March this year a novel iteration of the NCCN Prostate Cancer Early Detection guidelines was published (version 2.2024). With an overarching aim of maximising the early detection of significant aggressive prostate cancers and optimising discrimination from those with an indolent biology to optimise treatment to improve mortality while minimising morbidity associated with overtreatment of indolent disease this publication is intended to accompany the NCCN Guidelines for Prostate Cancer treatment recommendations. The three main sections of the guidelines cover baseline evaluation, risk assessment and early detection evaluation; further evaluation and indications for biopsy; and management of biopsy results.

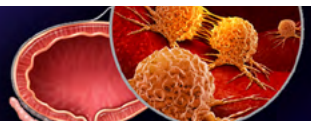
A synopsis of pertinent changes follows:

- Advice for repeat testing according to age has been modified to suggest annual or bi-annual testing for patients aged 40-75 years at high risk with PSA level ≤3 ng/mL, and every one-to-three-years in older patients
- Information regarding race-associated inequities in the prostate cancer incidence rate and mortality has been changed to reflect modernised understanding of the role of social determinants driving inferior outcomes in African American men, as opposed to the previously held belief that attributed survival disparities primarily to differences in the frequency of tumour acquired genomic variants. It is advised that PSA screening, with or without a digital rectal examination, for individuals considered high-risk (including African American men) commence from 40 years of age – five years before screening should start in individuals at standard risk for prostate cancer - albeit it is noted that there is little evidence demonstrating a mortality benefit to earlier age screening.

The complete and most recent version of these guidelines is available free of charge at www.NCCN.org

Earn CPD

Nursing and Midwifery Board of Australia (NMBA) Journal reading and watching videos (including Research Reviews') may be considered a self-directed activity set out in the NMBA Registration Standard: Continuing Professional Development. One hour of active learning will equal one hour of CPD. Details at NMBA CPD page.



First predictive test for therapy personalisation - ArteraAI – included in 2024 NCCN Guidelines® for prostate cancer

The latest NCCN Clinical Practice Guidelines for prostate cancer lists five advanced tools for the risk stratification of localised prostate cancer. Germline testing for homologous recombination deficiency (HRD) status has unclear prognostic value and no utility for prediction. There are three gene expression tools suitable for use in both the localised disease and post-radical prostatectomy settings - the 22-gene genomic classifier, the 17-gene Genomic Prostate Score assay and the 31-gene cell cycle progression assay (Prolaris®). These tests provide different prognostic information regarding metastasis, biochemical recurrence post prostatectomy and adverse pathology, amongst other things.

Now, a novel multimodal artificial intelligence tool – ArteraAI Prostate – has been included in the NCCN guidelines to provide more accurate risk stratification and inform therapy personalisation for patients classified as having any NCCN risk level of localised prostate cancer. ArteraAI is the first machine learning test to receive recommendation in these guidelines and the only tool to provide both predictive and prognostic information. The tool is supported by a Level 1B evidence rating per Simon Criteria and has a Category 2A recommendation, denoting it received a uniform consensus concerning its utility in this space. This instrument leverages a unique algorithm to combine clinical data and digital histopathology from prostate biopsy to predict absolute benefit from hormone and other treatment strategies and prognosticates long-term outcomes in patients. Validation of ArteraAI in post hoc analysis of five phase 3 trials and in individual trial subsets demonstrated superior discrimination of multiple oncologic endpoints including biochemical recurrence, distant metastasis, prostate cancer-specific mortality and overall survival, versus the three-tier NCCN risk group classification system. It should be noted that to date, specific score thresholds for specific treatments have not been established.

Incorporation of ArteraAI into clinical practice in the US has been supported by subsidy under Medicare & Medicaid services effective from January 1 this year, with out-of-pocket costs determined by each patient's insurance plan. The company has also secured substantial capital funding to support expansion of the test in the US and expand internationally. At the moment, the test is licensed in 48 US states and is available to order by licensed clinicians from the Artera laboratory in Florida online at Artera.ai. In Australia, accelerated access to the ArteraAI Prostate test is available to patients treated at GenesisCare clinics through a clinical trial. More information can be found here.

Press releases from Artera can be found here

^{64}Cu-SAR-bisPSMA may enable detection of small prostate cancer lesions

The radiotracer SAR-bisPSMA radiolabelled with copper-64 (^{64}Cu) may soon join the list of approved PSMA-PET diagnostic agents for the detection of prostate cancer lesions, with promising early phase results leading to a registrational phase 3 trial. ^{64}Cu-SAR-bisPSMA previously exhibited diagnostic accuracy for the detection of recurrent prostate cancer lesions after definitive therapy in a real-world compassionate use program and more recently, results from the first-in-human COBRA clinical study included detection of lesions in up to 80% of patients with biochemical recurrence with lesions undetectable by standard imaging and informed changes in treatment in approximately half. Now, additional data from COBRA released by Clarity Pharmaceuticals emphasises the utility of ^{64}Cu-SAR-bisPSMA to detect small prostate cancer lesions (<5 mm), suggesting it may even be a best-in-class PSMA-PET agent given the low sensitivity of existing imaging agents in this space. Briefly, men with suspected recurrence of prostate cancer based on rising PSA after radical prostatectomy, radiation therapy, cryotherapy, or brachytherapy with negative or equivocal findings on conventional imaging received a single administration of 200 megabecquerels ^{64}Cu-SAR-bisPSMA and underwent PET/CT scans on the same and next day. Further analysis of the data found that small lesions in the bone, pelvic and extra-pelvic lymph node regions were detected in 14% of the study population, with the smallest lesion measuring less than 2 mm. CLARIFY, a phase 3 registrational trial, will attempt to substantiate the diagnostic capability of ^{64}Cu-SAR-bisPSMA PET for the identification of regional node metastases in men with previously untreated, high-risk adenocarcinoma of the prostate who are scheduled for a radical prostatectomy with pelvic lymph node dissection.

The full press release from Clarity Pharmaceuticals can be found here

Regulatory News

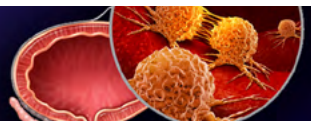
BXCL701 granted FDA fast track designation for treatment of small cell neuroendocrine prostate cancer

According to a news release from BioXcel Therapeutics, on February 12th the US Food & Drug Administration (FDA) granted a fast-track designation to the first-in-class oral innate immune activator BXCL701 as part of a combination regimen with immune checkpoint inhibition for patients with metastatic small cell neuroendocrine prostate cancer with progression on chemotherapy and no evidence of microsatellite instability.

Clinical proof of concept for inhibition of dipeptidyl peptidases with the small molecule BXCL701 plus pembrolizumab in patients with progressive disease after at least one prior line of systemic cytotoxic chemotherapy for locally advanced or metastatic disease was previously demonstrated in an ongoing phase 2, single-arm, open-label multicentre US trial (ClinicalTrials.gov Identifier: NCT03910660), with promising survival outcomes compared to historic data with checkpoint inhibitor monotherapy (median OS, 13.6 months; 12-month OS rate, 56%). Data presented at the 2023 Genitourinary Cancers Symposium further showed a composite response rate per RECIST v1.1 criteria of 20%, with a partial response the best response achieved, and a disease control rate of 48%.

In addition to the small cell neuroendocrine carcinoma phenotype of metastatic castration-resistant prostate cancer (CRPC), the trial has enrolled a cohort of patients with the adenocarcinoma phenotype. Survival outcomes reported so far in this later cohort include a median OS of 15.5 months and a 12-month OS rate of 59%.

The full press release can be read here



News in Brief

Funding granted to studies of relugolix in advanced prostate cancer

Pfizer Global Medical Grants and Sumitomo Pharma America have committed to provide over US$3.5 million in funding towards four investigator-initiated research studies of relugolix-based therapeutic regimens for advanced prostate cancer.

Per a NCCN news article, projects that successfully gained funding through a peer reviewed scientific review committee process include:

- Comeback from long-course ADT with relugolix and darolutamide in hormone-sensitive prostate cancer (CLEARED)
- Randomised controlled trial of leuprolide plus abiraterone acetate (AA) versus relugolix plus AA for advanced prostate cancer
- Optimising treatment and advanced multi-imaging response evaluation for very high-risk prostate cancer (OPTIMAL)
- Phase 1B trial of relugolix and enzalutamide as neoadjuvant/adjuvant to local-regional treatment in patients with high-risk locally-advanced prostate cancer

More information can be found here

Phase 2 study of PT-112 in mCRPC reached target enrolment

Promontory Therapeutics' phase 2 trial of PT-112, a small-molecule conjugate of pyrophosphate, for late-line metastatic castration-resistant prostate cancer has reached its target enrolment, according to a press release. A total of 109 men with progressive metastatic CRPC after at least three prior intended life-prolonging therapies for metastatic disease including androgen receptor directed therapy, chemotherapy or radioligand therapy and who lack any effective immunotherapy have been enrolled from the US and France. Top-line read-out data is expected late this year.

The press release can be found here

PSMA PET tracer piflufolastat (18F) available in Italy

Following the European Commission approval of marked authorisation to the PSMA-PET diagnostic agent ^{18}F-piflufolastat (Pylclari®; [18F]-DCFPyL) last year, it is now commercially available in Italy for the detection of PSMA-positive prostate cancer lesions. Local manufacture is currently located in Milan but will expand to Pisa and Rome. The agent is suitable for both primary staging of high-risk disease prior to initial curative-intent therapy and at time of suspected recurrence based on rising PSA levels.

The press release from Curium can be read here

Determinants of active surveillance uptake in a diverse population-based cohort of men with low-risk prostate cancer

The Treatment Options in Prostate Cancer Study (TOPCS) reports that almost 60% of men with low-risk prostate cancer chose active surveillance over definitive therapy and that while urologist recommendation strongly influenced this decision, patient decisional and psychological factors also play a role. The study included over 1600 men diagnosed between 2014 and 2017 in Detroit or Georgia in the US. Factors associated with a greater likelihood of choosing active surveillance included greater prostate cancer knowledge and a shared patient–physician treatment decision, while the desire for a cure or longer survival and a perception of a diagnosis as serious correlated with active treatment.

Cancer. 2024; Jan 22; Online ahead of print

COVID-19 Resources

Royal Australasian College of Surgeons
European Urology Journal
British Association of Urological Surgeons
American Urological Association
European Society of Medical Oncology
American Society of Clinical Oncology

Conferences, Workshops, and CPD

Please click on the links below for upcoming local and international prostate cancer meetings, workshops and CPD.

COSA – Events
MOGA – Events
USANZ – Events
COMS – Conferences and Meetings on Urology

Research Review Publications

Prostate Cancer Research Review with Professor Niall Corcoran and Professor Nathan Lawrentschuk

Urology Research Review with Professor Eric Chung

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